New approaches to assessing cardiovascular risk

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The authors discuss current evidence that links kidney disease, erectile dysfunction and cardiovascular disease. Appropriate screening and treatment strategies are likely to lead to a substantial reduction of the cardiovascular disease burden in patients with these common urological conditions.

Cardiovascular (CV) morbidity and mortality is an increasing clinical problem in patients with urological diseases. Several reasons account for this trend. First, CV and several urological conditions share common pathophysiological mechanisms and risk factors. Second, decreased renal function, commonly observed in urology practice, accelerates the evolution of CV disease, over and above the contribution of traditional CV risk factors. Third, better treatment of urological problems, resulting in increased survival, has unveiled underlying CV pathology.

CHRONIC KIDNEY DISEASE AND CV DISEASE

It has long been known that patients with clinical advanced chronic kidney disease (CKD) have markedly increased morbidity and mortality from CV complications. More recently, however, it has become clear that even modest reductions in renal function are associated with higher CV risk (Figure 1). With increasing longevity, 10–13 per cent of the general population has evidence of reduced renal function. Many will die from stroke, myocardial infarction or heart failure rather than end-stage renal failure (ESRF).

Figure 1. A modest reduction in renal function determines a significant increase in all-cause and cardiovascular mortality. Hazard ratios (HR) and 95 per cent confidence intervals (CI) for all-cause and cardiovascular mortality according to spline estimated glomerular filtration rate (eGFR) and albumin-to-creatinine ratio (ACR). HRs and 95 per cent CIs (shaded areas) according to eGFR (a, c) and ACR (b, d) adjusted for each other, age, sex, ethnic origin, history of cardiovascular disease, systolic blood pressure, diabetes, smoking and total cholesterol. The reference (diamond) was eGFR 95 ml/min per 1.73 m² and ACR 5 mg/g (0.6 mg/mmol), respectively. Circles represent statistically significant and triangles represent not significant.

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Foley et al., in a large Medicare database of 1 091 201 patients, showed an association between even mildly reduced renal function and CV disease burden. This has been confirmed by Go et al., who reported a substantial rise in CV events once the estimated glomerular filtration rate (eGFR) fell below 45–55ml/min per 1.73m². The early detection and lifetime management of preclinical CV disease in CKD patients is thus crucial for patient care. In addition, the presence of impaired renal function in cardiac patients is a major risk factor, which greatly elevates mortality after myocardial infarction.

Pathophysiology
A number of similar pathophysiological mechanisms underline the close relationship between CV and renal disease (Figure 2). Common conditions, such as diabetes, predispose to both and there are several shared risk factors. These include arterial hypertension, smoking and lipid disorders. In particular, elevated low-density lipoprotein and reduced high-density lipoprotein cholesterol are potent predictors for the development of CKD in both large population studies and meta-analyses.

Inflammation has emerged as a key pathway for CKD and CV disease, with increased levels of systemic inflammatory markers including C-reactive protein and other pro-inflammatory cytokines (IL-6 and TNF-alpha) frequently detected in patients with renal and/or vascular alterations. Furthermore, activation of the renin-angiotensin system (RAS), endothelin-1 (ET-1), endothelial dysfunction, oxidative stress and asymmetric ω-NG-dimethylarginine (ADMA) are detected early in the evolution of CV disease and CKD and actively contribute to the process of vascular remodelling.

In addition to classic CV risk factors, the consequence of disturbed renal function may contribute directly to the development of arterial disease and CV risk. Arterial calcification occurs in the intima as a consequence of atherosclerosis, but medial calcification (arteriosclerosis) occurs aggressively from an early age in CKD. This is secondary to disorders of mineral metabolism and results in increasing arterial stiffness (aggravating hypertension and its end-organ effects). The balance between FGF-23 and the membrane-bound protein Klotho becomes disturbed well before even a fall in GFR and recent evidence suggests this may contribute directly to endothelial dysfunction, left ventricular hypertrophy and CV risk.

Paradoxically, treatments for renal failure, such as dialysis, may greatly exacerbate these calcium-phosphate-related mechanisms for arterial disease and modified strategies for renal replacement therapies may reduce progression of arterial damage.

The development of microalbuminuria (MA) is a very sensitive and early manifestation of disturbed renal function. It is now clear, however, that it marks more generalised vascular damage and, in particular, the presence of systemic endothelial dysfunction and vascular permeability. These are important steps on the causal pathway for atherosclerosis. MA is present in a number of acute and chronic inflammatory conditions that are associated with increased CV risk, including obesity, diabetes and rheumatological diseases. Its detection should prompt screening for CV risk factors and introduction of multifactorial intervention strategies to prevent loss of renal function and to improve CV risk factor profile.

**Figure 2.** Metabolic factors, cardiovascular risk factors and inflammation are involved in the initiation and evolution of both atherosclerosis and chronic kidney disease. Once established, atherosclerosis actively contributes to the reduction of renal function. Similarly, a reduction in renal function induces faster progression of the arterial disease, particularly by promoting calcification of the media (arteriosclerosis) and increasing arterial stiffness. These reciprocal mechanisms greatly increase the risk of cardiovascular events.

ERECTILE DYSFUNCTION AND CV DISEASE
Presentation with erectile dysfunction (ED) is another important manifestation of increased CV risk. Diagnoses of ED more than doubled in the UK after sildenafil (Viagra) was introduced in common clinical practice. The growing number of people with an established diagnosis of ED has allowed better understanding of its strong connections with CV disease. It is now clear that ED shares modifiable risk factors with coronary and generalised vascular disease, including hypertension, diabetes, hyperlipidaemia, obesity, lack of physical exercise, cigarette smoking, poor diet, excess alcohol intake and psychological stress. Furthermore, a significant proportion of men with ED show early signs of coronary artery disease and have more rapid progression. It is thus essential to regard patients with ED as candidates for CV morbidity and mortality.

A number of studies have demonstrated that CV disease and ED share common pathophysiological mechanisms. It is believed that normal erectile function requires endothelial integrity, optimal relaxation of the cavernous smooth muscle with increase in the arterial blood flow and decrease in venous outflow. In the presence of CV risk factors, increased inflammation and oxidative stress result in endothelial dysfunction and promote diffuse atherosclerotic arterial changes.
Chiurlia et al. demonstrated that the presence of ED in asymptomatic individuals was strongly associated with subclinical arterial atherosclerotic changes. Particularly, flow-mediated dilation of the brachial artery, which is currently considered the non-invasive, gold-standard technique to measure endothelial dysfunction, was significantly reduced in patients with ED compared to healthy controls. Similarly, measures of coronary artery remodelling, such as coronary artery calcification, were more frequently detected in individuals with ED than in control subjects.

Because ED might represent an early manifestation of an ongoing underlying CV disease, it has the potential to add incremental information to common scores used for CV risk prediction. In a meta-analysis of 12 studies, which included 36,744 patients, Dong et al. documented that ED may significantly increase the risk of coronary artery disease and all-cause mortality, independently from conventional CV risk factors. Furthermore, as penile arteries are smaller than coronary arteries, manifestations of ED are likely to precede symptoms of coronary artery disease. Therefore, diagnosis of ED might provide an opportunity to identify preclinical disease in men whose high risk for CV events would not otherwise be recognised.

The COBRA (AsscoCiatiOn Between eRectile dysfunction and coronary Artery disease) study investigated the relationship between ED and coronary atherosclerosis. The level of coronary atherosclerotic burden was evaluated on the basis of clinical manifestations (chronic versus acute coronary syndrome) as well as with coronary angiography (Gensini score). Results demonstrated that prevalence of ED was significantly higher in patients with chronic compared with acute coronary syndromes and the severity of ED was significantly higher in patients with multivessel than in those with single-vessel disease. Remarkably, 93 per cent of patients with a chronic coronary syndrome reported ED symptoms before the onset of angina pectoris, with a mean interval of 24 (range 12–36) months. Furthermore, there was a significant relationship between the length of time from ED to coronary artery disease onset and the number of vessels involved.

Similar results were obtained in the Olmsted County Study, which also showed that the ability of ED to predict clinical manifestations of CV disease is higher in younger (40–49 years old) than older individuals. As a result, it is essential to regard young individuals with ED as highly likely candidates for future CV events; ED has recently been recognised as an independent marker of increased risk for CV disease by the American College of Cardiology Foundation/American Heart Association. The interval between presentation with ED and development of CV complications represents an opportunity for risk factor reduction, and lifestyle and pharmacological interventions.

**SCREENING FOR CV DISEASE IN PATIENTS WITH CKD AND ED**

All men with ED should have a comprehensive screening for CV risk factors (including glucose, lipid and blood pressure [BP] levels) and for evidence of preclinical vascular disease. American and European guidelines for CV disease prevention advise the use of carotid intima-media thickness, aortic stiffness and computed tomography scans to quantify coronary artery calcium in high- to intermediate-risk subjects. These surrogate markers of atherosclerosis reflect the burden of vascular damage in a given individual and therefore are likely to provide the greater improvement in CV risk stratification to the currently used CV scoring systems.

In the general population, CV prevention is moving towards earlier screening. Similar approaches should be adopted in individuals with CKD and ED. The health-check programme recommends regular health checks starting from the age of 40 years. This is appropriate as from this age there is an accelerated decline in renal function (GFR decreases by around 0.751 ml/min per year) and the emergence of ED.

It is important to note that CV prevention guidelines are based largely on 10-year risk estimates and thus do not adequately deal with younger subjects. The presence of CKD and ED, especially in men aged 30–60 years, is an indicator of increased CV risk independently of the score obtained from current CV risk prediction charts, and justifies risk factor treatment.

**TREATMENTS**

Management of patients with ED and CKD should focus on reduction in CV risk factors, as this is likely to reduce the risk of not only CV complications but also urological symptoms. This should include both lifestyle and pharmacological approaches. There is a wealth of data supporting superiority of early rather than late management of CV risk factors for improving CV outcome in patients with erectile and renal dysfunction.

**Lifestyle interventions**

Weight reduction and increased physical activity have been shown to improve symptoms of ED. In a single-blind randomised trial including 110 obese individuals, Esposito et al. demonstrated that increased levels of physical activity result in a significant reduction of body mass index and are associated with a parallel improvement of inflammatory markers and severity of ED, using the International Index of Erectile Function (IIEF) score. In multivariate analyses, changes in body mass index, physical activity and C-reactive protein were independently associated with changes in IIEF score. White and colleagues reported that a nine-month exercise intervention (60 min/day, ~3.5 days/week at 75–80 per cent maximum aerobic capacity) significantly enhanced the frequency of intercourse and orgasms, and maintained erections, as recorded in sexuality diaries of the exercising group compared to a control group who were prescribed a low-intensity walking programme.

Beneficial effects of physical activity are also observed in patients with CKD. A recent systematic review of the Cochrane database identified 45 studies, randomising 1863 participants, which explored the health effects of physical exercise intervention (eight weeks or more) in patients with CKD. The analyses...
showed that there is evidence for significant beneficial effects of regular exercise on physical fitness, walking capacity, health-related quality of life and some CV (eg BP and heart rate) and nutritional parameters in adults with CKD.

Lipid-lowering therapy

Apart from lifestyle approaches, recent evidence highlights opportunities for pharmacological treatment of CV risk factors in patients with CKD and ED. In particular, lipid-lowering therapies have been shown to be effective in reducing cardiac death and atherosclerosis-mediated CV events.

The SHARP trial is the first to demonstrate conclusively the benefits of a statin/ezetimibe combination in 9270 patients aged 40 years or older with CKD. After a median follow-up of 4.9 years, there was a significant lower rate of major CV events in patients treated with simvastatin plus ezetimibe (11.3 per cent) than in those receiving placebo (13.4 per cent; Figure 3). The findings of this important trial are supported by two recent meta-analyses. In particular, Palmer et al. summarised the benefits and harms of statin therapy for adults with CKD and examined whether effects of statins vary by stage of kidney disease. The meta-analysis included 80 trials comprising a total of 51099 participants. Importantly, the benefits of statin therapy are evident in subjects with mild to moderate CKD but not in those receiving dialysis (as in the 4D trial), strongly supporting early initiation of statin treatment in CKD.

There are a number of reports of improved erectile function in men receiving statins with and without phosphodiesterase-5 (PDE5) inhibitors, but a recent report showed a high rate of new-onset ED (22 per cent of 93 men after six months of statin use) in subjects with high CV risk, suggesting that late initiation of statin in older patients with comorbidities such as diabetes and multiple CV risk factors may be less effective.

Antihypertensive agents

Blood pressure is another important modifiable CV risk factor in patients with CKD and in those presenting with ED. However, a number of important issues remain unresolved, including the optimal target level of BP in different populations, differences between antihypertensive agents, and the potential for treatment-related adverse effects on renal function, ED and CV outcome.

Most current guidelines recommend a BP goal of equal to or less than 130/80 mmHg in patients with impaired renal function. There is, however, little evidence to support this ambitious target. The recent Action to Control Cardiovascular Risk in Diabetes Blood Pressure (ACCORD BP) trial showed no benefit from intensive, over standard, BP control on progression of CKD in type 2 diabetic and hypertensive patients, regardless of their glycaemic control. These results are in line with the negative findings of the earlier ACCORD analyses. The advanced vascular disease that underlines hypertension in CKD makes it difficult to achieve BP targets and increases the risk of progression of disease and/or adverse events associated with antihypertensive therapies. This again argues in favour of earlier treatment in view of the disappointing results from large-scale trials in advanced disease.

Evidence is emerging that it is the ability to control BP, rather than the choice of antihypertensive agents, that determines outcome. The British Hypertensive Society guidelines are based on BP-lowering efficacies at different ages. In diabetes and CKD there may be specific advances for RAS blockade, particularly in young subjects, as shown in numerous trials of proteinuria progression. These agents, however, should be used with caution in all patients with advanced atherosclerosis and potential ischaemic renal pathology. Comparisons between classes of BP-lowering drugs are less relevant in patients with CKD, as most will require combination therapies to achieve acceptable levels of BP. In contrast, in patients with ED, while benefits of BP lowering are established, the choice of agent may affect ED symptoms. For example, beta-blockers may adversely affect ED, and nebivolol, which has direct vasodilating properties, may be the agent of choice in these circumstances. Similarly, angiotensin-receptor blockers and angiotensin-converting enzyme inhibitors are less likely to cause ED than other antihypertensive agents (such as diuretics).
experience this has not proved to be the case, as shown by the second Princeton Consensus Conference recommendations and analyses of placebo-controlled and post-marketing surveillance data (provided co-administration with nitrates is avoided). Indeed, recent trials have suggested a role for PEDS inhibition in the management of hypertension and endothelial dysfunction in patients at risk for CV disease.

CONCLUSIONS

It is now clear that patients presenting to urologists are often at high risk from CV disease, in spite of effective treatment of renal disease and symptoms such as ED. It is therefore important to undertake comprehensive assessment of CV risk, including a search for subclinical markers of arterial disease. This should be done at presentation, as evidence is accumulating for substantial outcome benefits from lifestyle and pharmaceutical interventions, particularly when they are initiated early. Increasing collaboration between GPs, urologists and cardiologists will lead to better understanding of common mechanisms of disease and new opportunities to improve patient outcome.

Declaration of interests: none declared.

REFERENCES
